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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,521	06/24/2005	Hirotaka Haro	Q94277	5337

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
4161	

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06/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,521	HARO, HIROTAKA	
	Examiner	Art Unit	
	PAUL ZAREK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/24/2005, 02/12/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-4 have been canceled by the Applicant. Claim 5-8 were added in a correspondence submitted on 06/24/2005. Claims 5-8 are currently pending. This is the first Office Action on the merits of the claim(s).

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Claim Objections

3. Claims 6-8 are objected to because of the following informalities: Claims 6-8 are dependent upon Claim 1, which has been canceled by Applicant. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diseases associated with a herniated disc or herniated nucleus pulposus with extracellular matrix proteases, does not

reasonably provide enablement for a method of treating a disease associated with lumbago, discopathy, or spondylosis. Further, treatment of any degenerative intervertebral disc by a protease other than a human-derived extracellular matrix protease is not enabled. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

A. *The breadth of the claim*: The claims are drawn to a method of treating diseases associated with a degenerative intervertebral disc, comprising administering a human-derived protease to the affected site. The degenerative intervertebral disc may be caused by a herniated disc, lumbago, discopathy or spondylosis;

B. *Nature of the invention*: The nature of the invention is a method of treating diseases associated with degenerative intervertebral discs;

C. *The state of the prior art*: The prior art teach that matrix metalloproteases (MMPs) may be effective treatments when degenerative nucleus pulposus ruptures the fibrous tissue and protrudes into the spinal canal to compress the nerve root (Haro, et al, Spine, 1997). Intravertebral injections are well known and routinely performed. Lumbago may be caused not only by degenerative intervertebral disc, but also by disorders unrelated to degeneration of the

intervertebral discs, such as external injury or tumor. Discopathy is an exceedingly general term to describe a disease of an intervertebral disc. Spondylosis is generally applied nonspecifically to any lesion of the spine of a degenerative nature. Discopathy and spondylosis are not necessarily caused by degeneration of intervertebral discs.

Human-derived proteases encompass are a wide and diverse range of enzymes including metalloproteases (of which extracellular matrix proteases are a part) serine proteases, threonine proteases, cysteine proteases, aspartic acid proteases and glutamic acid proteases. The proteases have specific targets which do not necessarily overlap;

D. *Level of one of ordinary skill in the art*: Physicians and scientists familiar with the causes and treatments of herniated disc or herniated nucleus pulposus would be one of ordinary skill in the art;

E. *Level of predictability in the art*: Human-derived proteases, in general, and extracellular matrix metalloproteases, in particular, are well known, can be reliably isolated and purified. The ability of extracellular matrix proteases to ameliorate herniated nucleus pulposus is well known;

F. *Amount of direction provided by the inventor*: Inventor demonstrates the ability of MMPs to be an effective treatment for degenerative intervertebral disc caused by a herniated disc or herniated nucleus pulposus. No comment is made regarding the ability of MMPs to treat lumbago, discopathy, and/or spondylosis due to conditions other than a herniated disc or herniated nucleus pulposus. No comment is made regarding the ability of a human-derived protease other than

extracellular matrix proteases as an effective treatment for degenerative intervertebral disc caused by a herniated disc or herniated nucleus pulposus;

G. *Existence of working examples*: All working examples provided by Applicant demonstrate the ability of MMP-3 or MMP-7 to treat rupture of a degenerative nucleus pulposus. The Applicant provides no working examples of using MMP's to treat discopathy, spondylosis or lumbago that are not caused by the rupture of a degenerative nucleus pulposus. Applicant provides no working examples of using a human-derived protease other than MMP-3 or MMP-7 to treat a rupture of degenerative nucleus pulposus; and,

H. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Discopathy, spondylosis or lumbago that are not caused by the rupture of a degenerative nucleus pulposus would not necessarily be receptive to treatment by a human-derived protease. For example, lumbago may be caused by tumors, which are notoriously difficult to treat. In the absence of any working examples, undue experimentation would be required of one of ordinary skill in the art to be enabled to use the claimed invention to treat discopathy, spondylosis or lumbago that is not caused by a herniated disc or herniated nucleus pulposus.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 5, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Haro, et al (Spine).

9. Claims 5, 7, and 8 of the Instant Application are drawn to a method of treating a disease associated with degenerative intervertebral disc with a human-derived protease (Claim 5). The protease may be an extracellular matrix protease (Claim 7) or be further limited to a specific extracellular matrix protease (Claim 8). Haro, et al., teach a method of treating rats in which the normal nucleus pulposus from the tail was obtained, injected with rh-stromelysin-1 (aka MMP3), and grafted into the abdominal subcutaneous tissue of the same animal (pg 1099, final paragraph). Haro, et al., have treated a degenerative intervertebral disc by administering a human-derived protease (MMP-3) to the affected site (abdominal subcutaneous tissue) of a disease associated with a degenerative disc (experiment-induced nucleus pulposus). Therefore, Haro, et al., anticipate all the limitations of Claims 5, 7, and 8, of the Instant Application.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5-8 rejected under 35 U.S.C. 103(a) as being unpatentable over Einarson, et al. (Drug Intelligence and Clinical Pharmacy, 1984), in view of Haro, et al. (Spine,), and Haro, et al. (Journal of Spinal Disorders, 1999).

12. Claims 5-8 of the Instant Application are drawn to a method of treating diseases associate with a degenerative intravertebral disc by administering to the affected site a human-derived protease. The disease may be lumbago, discopathy or spoldylosis (Claim 6). The protease could be generally an extracellular matrix protease (Claim 7), or a specific matrix metalloproteases (MMP, Claim 8). The prior art teach that a herniated disc is caused when the fibrous tissue ruptures and the nucleus pulposus protrudes into the spinal canal. There is a natural resorption mechanism by which the nucleus pulposus retreats within the disc, alleviating the pressure on the nerves within the spinal canal. Einarson, et al., teach that degradation of the non-collagenous, extracellular protein by direct administration of chymopapain is an effective treatment for herniated discs (pg 561, subheading "Pharmacology"). Chymopapain treatment enhances the resorption process to speed the reduction of the volume of the herniated disc. More generally, Einarson, et al., demonstrates that it is both feasible and effective to treat a herniated disc with a direct administration of an agent that can break down the extracellular matrix, and speed resorption of the nucleus pulposus into the disc. Einarson, et al, is silent with respect to human-derived proteases.

Haro, et al. (Spine), teach the treatment of herniated nucleus pulposus with human stromelysin-1 (MMP3). Both *in vitro* and *in vivo*, Haro, et al., demonstrated that MMP-3, injected into the murine nucleus pulposus tissue, rapidly reduced the size of the herniated disc. Haro, et al., teach that ". . . stromelysin-1 at a low concentration may still prove

effective in degrading cartilaginous matrix of HNP [herniated nucleus pulposus] . . . " (pg 1103, 1st paragraph). Haro, et al. (J. Spinal Disorders), teach that both MMP-7 and MMP-8 may play a role in the resorption process. Haro, et al., further teaches "[t]he use of human enzymes involved in the resorption process of HNP may physiologically facilitate the matrix degradation, avoiding complications. We assume metalloproteinases expressed in the HNP tissues are potential candidates for use in chemonucleolysis." (pg 248, final paragraph) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat herniated discs by modifying the method taught in Einarson, et al., by replacing chymopapain with MMP-3, 7 or 8. Haro, et al. (Spine), teaches the effectiveness of using human stromelysin-1 (MMP-3), thereby demonstrating that human MMPs can be readily utilized with a reasonable expectation of success.

Conclusion

13. No Claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is (571)270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK NOLAN can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Ashwin Mehta/
Primary Examiner, Technology Center 1600